REMARKS

In response to the Office Action mailed January 11, 2008, reconsideration of the application is respectfully requested in view of the pending claims and the following remarks. Claims 1, 53-55, and 57-71 are pending in this application. Claims 2-52 and 56 were cancelled previously.

Claims 1, 57-59 and 67 are amended, new claims 72-78 are added herein. Support for the amendments and new claims are found in the specification, for example, page 10, lines 15-28, and page 18, lines 26-27 which provides for "an analyte binding moiety (e.g., an antibody or antigen) ... dried into (or otherwise localized in) ... a lateral flow chromatography strip..."

No new matter is introduced by these amendments.

Rejections Under 35 U.S.C. § 112, First Paragraph

On page 2 of the Office Action, the Examiner rejects claims 1, 53-55, and 57-71 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the written description requirement." In particular, the Examiner alledges that in claims 1 and 67 the words "*planar flow communication*," are not recited in the specification. Applicants respectfully traverse the rejection. Nevertheless, in an effort to expedite prosecution, Applicants have amended the claims to recite "*fluid communication*."

That the blocking pad is in fluid communication with the capillary matrix, and that the lateral flow chromatography strip is in fluid communication with the capillary matrix is clear from the specification. For example, referring to the published application, 20020192839, paragraph [0013] notes that:

> the apparatus comprises a capillary matrix having exposed a surface for receiving oral fluid; and a lateral flow chromatography strip where the lateral flow chromatography strip is in *communication* with the capillary matrix such that when the capillary matrix receives oral fluid, the capillary matrix *wicks up the oral fluid and delivers* the oral *fluid* to a receiving area of said lateral flow chromatography strip.

[0015] recites that:

> the capillary matrix, when contacted to an oral mucosa takes up oral *fluid* from said oral cavity and readily *releases* the oral fluid to said receiving area of said lateral flow chromatography strip.

language at [0019] explains that:

> a hydrophilic capillary matrix is provided as a transport for oral *fluids* to a lateral chromatographic strip. The lateral chromatographic strip is placed within a cavity defined in a housing and is disposed along the housing to an inspection site. A hydrophilic capillary matrix protrudes from the housing to an oral collection site exterior of the housing at one end and *communicates* to the lateral chromatographic strip at the other end. ... Interstitial matrix dimension is such that forces of capillary action cause the immediate *drawing* of materials into the hydrophilic capillary matrix. The hydrophilic capillary matrix readily releases oral *fluid* to the lateral chromatographic strip.

Referring to the method of using the claimed device:

> [0020] The method involves the steps of: i) inserting into the oral cavity of a mammal any of the oral fluid assay apparatuses described herein such that the capillary matrix is contacted with an oral mucosal surface whereby the capillary matrix *wicks up* oral *fluid* and *delivers* the oral *fluid* to a receiving area of a lateral flow chromatography strip.

According to [0029], "The term 'wick up' is used to refer to the uptake of a *fluid* predominantly by adsorption and capillary action." Accordingly:

> [0044] The capillary matrix acts as a receiving body or pad that rapidly absorbs (wicks up) oral fluid, e.g., via capillary action, and delivers that oral fluid to a lateral flow immunochromatography strip (e.g., C in FIG. 1).

Additionally, the specification states that:

> [0053] In addition to rapidly taking up and transporting the oral *fluid* to the lateral flow chromatography strip, the capillary matrix material is selected that preferably readily *releases* the fluid to the chromatography strip. This should be accomplished rapidly without compression of the matrix material itself. Thus, in a preferred embodiment, the *capillary matrix delivers and releases oral fluid to the lateral flow chromatography strip* with no manipulation (e.g. no squeezing or compression of the capillary matrix).
>
> [0054] From the foregoing, it should be clear that preferred capillary matrix materials have an interstitial spacing that facilitates uptake of oral fluid through capillary attraction in combination with adsorption on the material. This causes the oral fluid gathered from the mouth to be transported to the lateral chromatographic strip in preference to remaining in the mouth. At the same time, when the oral fluid arrives at the lateral chromatographic strip, it is absorbed to the strip in preference to remaining in the capillary matrix.

Moreover, relating to the fluid communication between the blocking pad and the lateral flow chromatography strip, "[0088] The blocking pad can be composed of a wide

variety of materials as long as they do not impede *flow* of oral *fluid* from the capillary matrix to the lateral flow chromatography strip."

Finally, the specification instructs that:

> [0095] FIGS. 1, 2, and 3 illustrate various embodiments of the assay device of this invention. Lateral flow chromatography or immunochromatography strip (C) is disposed lengthwise within housing (H). One end of the chromatography strip contacts directly, or by way of blocking pad (B) with a portion of capillary matrix (W). The capillary matrix (W) projects out of the housing (H) where it presents a face (3) that acts as an absorbant surface for uptake of oral fluid. The oral *fluid migrates through the matrix* (W) and through blocking pad (B) if present, where it is finally delivered to a receiving area (R) on the lateral flow chromatographic strip.

There is no requirement for a *verbatim* description of every claimed embodiment. When deciding whether a disclosure satisfies the written description requirement with regard to a specific claim, it is proper to examine the application as a whole to decipher what it conveys to one of skilled in the pertinent art. *See, e.g.*, *In re Edwards*, 568 F.2d 1349, 1351-52 (CCPA 1978) (citing *In re Lukach*, 442 F.2d 967 (CCPA 1971)). It is clear from the specification that the blocking pad is in communication with the capillary matrix, and the lateral flow strip is in communication with the capillary matrix, and that this communication allows the fluids to move from one to area to the next. Applicants urge that "fluid communication" is adequately supported by the specification at hand.

On page 3 of the Office Action, the Examiner asserts that "Claims 1 and 67 are also not supported by the specification with respect to the recitation of a '*non-absorbing*' capillary matrix." More specifically, the Examiner notes correctly that the specification recites "a capillary matrix that is *essentially non-absorbing*." The Examiner mistakenly alleges that the specification, at page 21 lines 16-18, recites that the capillary matrix "is" an absorbent surface for the uptake of oral fluid. Instead, this reads:

> The capillary matrix (W) projects out of the housing (H) where it presents a face (3) that ***acts*** *as* an absorbant surface for uptake of oral fluid. The oral fluid migrates through the matrix (W) and through blocking pad (B) if present, where it is finally delivered to a receiving area (R) on the lateral flow chromatographic strip.

Applicants invite the Examiner to understand that although the above quote provides a general description of the action of the capillary matrix, it does not refer to the nature of the

capillary matrix itself. Nevertheless, in an effort to expedite prosecution, the Applicants have amended the claims to recite "essentially non-absorbing," which is supported by the specification as follows:

> [0019] More particularly, a hydrophilic capillary matrix is provided as a transport for oral fluids to a lateral chromatographic strip. The lateral chromatographic strip is placed within a cavity defined in a housing and is disposed along the housing to an inspection site. A hydrophilic capillary matrix protrudes from the housing to an oral collection site exterior of the housing at one end and communicates to the lateral chromatographic strip at the other end. This hydrophilic ***capillary matrix defines a matrix of passageways defined between non-absorbent materials***, such a either plastic spheres or foams. The exterior surfaces of the matrix are hydrophilic by either being naturally hydrophilic or treated to be hydrophilic. Interstitial matrix dimension is such that forces of capillary action cause the immediate drawing of materials into the hydrophilic capillary matrix. The hydrophilic capillary matrix readily releases oral fluid to the lateral chromatographic strip. Prevention of reverse flow to the oral cavity from the lateral chromatographic strip naturally occurs due to the circuitous flow path of the porous wick material. By observing the lateral chromatographic strip while the entire test device is in the mouth immediate test results are obtained.
>
> [0028] The terms "capillary matrix" or "porous matrix" are used herein to refer to a highly porous material characterized by a pore size sufficiently small that the material rapidly takes up aqueous solution (e.g. of oral fluid) ***predominantly*** by capillary action or "wicking".
>
> [0047] The capillary matrix (porous matrix) material is preferably selected to provide a number of unique properties to the assay device. Such properties include, but are not limited to, a relatively low void volume, a pore size sufficient to provide rapid and effective delivery of the oral fluid to the test strip, low or non-reactivity with the oral fluid or analytes, easy release of the oral fluid to the immunochromatography test strip, and a non-deformable (when wetted) collection pad.
>
> [0048] Because oral fluid may be in short supply (patients often suffer a "dry mouth" during testing) it is desirable to maximize the amount of oral fluid that is transported from the oral cavity (e.g., the oral mucosa) to the lateral flow chromatography strip. This is accomplished by the use of a capillary matrix having a minimum void volume. The capillary matrix should have a void volume less than about 65%/cm^3, preferably less than about 57%/cm^3, more preferably less than about 48%/cm^3, and most preferably less than about 40%/cm^3, 35% cm^3, or even 25% cm^3. Capillary matrices having such low void volumes typically deliver a significant amount of the absorbed oral fluid to the lateral flow chromatography strip.
>
> [0049] The matrix itself must be of relatively small dimension. Specifically, the interstices is preferably of a dimension where capillary forces cause the fluid to be drawn into the capillary matrix. Thus, the capillary matrix is also selected to have an

average pore size small enough to provide rapid uptake of the oral fluid with which it is contacted (e.g., via capillary action). The small pore size also functions to exclude particulate material present in the fluid sample. The pore size, however, is also selected to be large enough that the viscous oral fluid does not clog the capillary matrix and instead rapidly transports through the matrix to the lateral flow chromatography pad. Preferred materials have an average pore size that ranges from about 40μm to about 250μm, more preferably from about 60μm to about 200μm, and most preferably from about 80μm to about 120μm.

[0050] In addition to having a pore size (channel size) that results in rapid uptake of the oral fluid, the surfaces of the capillary matrix should be chemically compatible with rapid uptake of the oral fluid. Thus, preferred capillary matrix materials are themselves hydrophilic or treated to be hydrophilic (eg. by addition of a surfactant also referred to as a detergent or wetting agent). That is to say, water must flow on and be attracted to the surfaces of these materials.

[0051] While a number of suitable materials are naturally hydrophillic (e.g. clean scintered glass or fused glass beads), other suitable materials (e.g., plastics) are typically hydrophobic (e.g., do not easily wet). However, such hydrophobic materials can be routinely treated with a wetting agent (i.e., surfactant/detergent) and thereby rendered hydrophilic (wettable). However, since the capillary matrix is used in the oral cavity, it is required that the treating detergent be known not to be harmful to the subject mammal (e.g., human body) and preferably be approved for such use by the relevant regulatory authority (e.g., Food and Drug Administration). In one preferred embodiment, a porous plastic material (e.g., polyethylene or polypropylene foam) can be rendered hydrophilic by taking the untreated matrix material and placing it in a dilute aqueous solution of an approved detergent such as sodium N-methyl cocoyl taurate. Thereafter, the treated material is dried, leaving the surfaces of the matrix apparently thinly coated with the detergent.

[0052] While N-methyl cocoyl taurate is preferred, it will be appreciated that other detergents can as well be used. It is only required that the detergent by safe for mammalian oral exposure, not interfere with the test on lateral chromatographic strip C, and produce the required hydrophilic properties on the exterior surfaces of the matrix.

[0053] In addition to rapidly taking up and transporting the oral fluid to the lateral flow chromatography strip, the capillary matrix material is selected that preferably readily releases the fluid to the chromatography strip. This should be accomplished rapidly without compression of the matrix material itself. Thus, in a preferred embodiment, the capillary matrix delivers and releases oral fluid to the lateral flow chromatography strip with no manipulation (e.g. no squeezing or compression of the capillary matrix).

[0054] From the foregoing, it should be clear that preferred capillary matrix materials have an interstitial spacing that facilitates uptake of oral fluid through capillary attraction in combination with ***adsorption*** on the material. This causes the oral fluid gathered from the mouth to be transported to the lateral chromatographic strip in preference to remaining in the mouth. At the same time, when the oral fluid arrives at the lateral chromatographic strip, it is absorbed to the strip in preference to remaining in the capillary matrix.

[0055] In a preferred embodiment, the hydrophilic capillary matrix is an ***essentially non absorbing matrix*** which ***adsorbs*** liquid via capillary action. In such

adsorbtion, the volume of the material is not appreciably effected. In addition, the capillary matrix material is relatively rigid such that its morphology remains essentially unchanged during the assay (e.g. when saturated with oral fluid). Thus, saturation of the matrix with an oral fluid does not substantially alter the average pore size or void volume of the porous matrix. In addition, saturation of the capillary matrix with an oral fluid results in a volume change of less than 30%, preferably less than 25%, more preferably less than 20% and most preferably less than about 15%, 10%, 5% or less than about even 1%.

[0056] In a particularly preferred embodiment, the capillary matrix can act as a barrier to back flow of reagents from the lateral flow chromatography strip back into the capillary matrix. This can be accomplished, for example, where the chromatography strip has a larger volume for fluid storage than the capillary matrix. In addition or alternatively, where the lateral flow chromatography strip is more hydrophilic than the capillary matrix the capillary matrix can also act as a barrier to backflow.

[0057] The capillary matrix materials are selected such that they are not chemically reactive with either the oral fluid or the analytes contained therein. Matrix materials compatible with oral fluid are well known to those of skill in the art are include, but are not limited to glass, resins, and various plastics.

[0058] In one preferred embodiment, the properties described above are achieved by the use of porous plastic materials for the capillary matrix. Suitable porous plastic materials include, but are not limited to, porous matrices of high density polyethylene (HDPE) ultra-high molecular weight polyethylene (UHMW), polypropylene (PP), polyvinylidene fluoride (PVDF), polytetrafluoroethylene (PTFE), nylon 6 (N6) and polyethersulfone (PES). In a preferred embodiment, the porous matrix materials are either themselves hydrophilic (so as to readily uptake the oral fluid) or are treated (e.g., with a surfactant/detergent) so as to be hydrophilic.

[0059] Such porous plastics are commercially available (see, e.g., Porex Technologies, Fairbum, Ga.). Particularly preferred porous plastics are detergent surfactant) treated polyethylene and/or polypropylene. The treatment typically involves soaking the capillary matrix in a surfactant/detergent and then allowing it to dry naturally or force drying the material.

[0060] Particularly preferred porous matrix materials are Porex X-4588, 80-120μm pore size at 0.024 inches of thickness made from polypropylene. Likewise, Porex X-4903 at 0.0.0625 inches, pore size 45-90μm, and Porex X-4913 at 0.0625, pore size 90-130μm are suitable. In one preferred embodiment, these materials are treated with sodium N-methyl cocoyl taurate. The capillary matrix materials are soaked in the detergent which is then dried onto the surface comprising the porous matrix.

[0061] It will be understood that the Porex7 materials that are utilized do not retain large volumes of the oral fluid. ...

[0063] At the same time, hydrophilic ***capillary matrix W does not have a high relative retention of the oral fluid***. For example, it readily surrenders its fluid to lateral chromatographic strip C and absorbent pad A. ***It will be understood that hydrophilic capillary matrix W acts more as a conduit than as an absorbent; material is readily discharged from the wick.***

As can be seen from the detailed recitations presented above, that the claimed capillary matrix is essentially non-absorbing is adequately supported by the specification. Applicants request that the § 112 rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

On page 4 of the Office Action, the Examiner rejects claims 57-59 under 35 U.S.C. § 112, second paragraph, as "indefinite" because they recite the intended use of the device rather than a positive limitation of the device itself. More specifically, the Examiner asserts that "these claims do not recite the specific reagents that would be required to detect the various analytes." Applicants traverse the rejection. Nevertheless, claims 57-59 have been amended to recite that the reagent is an antibody to or an antigen of the recited analytes. In addition, for the Examiner's consideration, new claims 72-74 specify that the reagent is an antigen, and new claims 75-77 specify that the reagent is an antibody. It is clear from the specification that the reagent may be an antibody or an antigen:

> [0023] As used herein, the term "analyte" is used to refer to a moiety that is to be detected in a particular assay. Analytes can be atoms (elements), molecules, or groups of molecules. Analytes commonly detected in the assays of this invention include, but are not limited to antibodies, antigens, growth factors, enzymes, therapeutic drugs, drugs of abuse, and the like. Particularly preferred analytes ***include antibodies and antigens*** relevant to infectious and non-infectious disease.
>
> [0036] As used herein, an "immunoassay" is an assay that utilizes ***an antibody or antigen to specifically bind to the analyte***. ...
>
> [0077] Typically, the strip will include means for immunospecifically binding the analyte to be detected with its specific ***binding partner*** (e.g., where ***the analyte is an antigen, the binding partner is an antibody or antibody fragment, and vice versa***) which bears a detectable label....
>
> [0080] Many lateral flow immunochromatography systems utilize particulate (microparticle) markers (e.g., gelatin, dyed latex, or colloidal gold) which are labeled with a binding partner (***e.g., antibody or antigen***) that binds the analyte of interest.
>
> [0081] The microparticles or other detectable moieties attached to an analyte binding moiety (***e.g. an antibody or antigen***) are dried onto (or otherwise localized in) ....

Applicants respectfully submit that claims 57-59 are no longer indefinite. Reconsideration and withdrawal of the § 112 rejection of these claims is requested.

Rejections Under 35 U.S.C. § 103(a)

On page 4 of the Office Action, the Examiner rejects claims 1 and 53-55 and 57-71 under 35 U.S.C. §103(a) "as being unpatentable over May (US 5,622,871) in view of Schlipfenbacher (US 5,160,486)." Applicants traverse the rejection.

In particular, the Examiner notes that "May differs from the instant invention in failing to specifically teach a separate blocking strip and a conjugate strip between the collection strip and an assay strip." Office Action at 6. May fails, however, to provide ***any*** blocking synonymous with that of the claimed invention, and thus would provide no reason to combine May with Schlipfenbacher.

The claimed apparatus for collection and lateral flow chromatography of oral fluid, in particular, features a lateral flow chromatographic strip, a blocking strip coupled between the capillary matrix and the lateral flow chromatographic strip, wherein the blocking strip impregnated with at least one blocking agent. In particular, the invention includes a blocking strip within the housing coupled between and in fluid communication with the capillary matrix and the lateral flow chromatography strip, wherein the blocking strip is impregnated with at least one blocking agent which reduces non-specific binding on the lateral flow chromatography strip.

As the Examiner notes, May does not teach a blocking strip. The portion of May cited by the Examiner, col. 16, line 67 to col. 17, line 40, describes the preparation of a labeled antibody reagent, Anti-hCG-Dye Sol, a process in which protein may be coupled to a dye sol by passive absorption. May uses a blocking agent to block excessive binding sites in the sol, after the antibody protein is added. The antibody-sol conjugate is separated from the solution by centrifugation and freeze dried for use:

> (A) Anti-hCG-Dye Sol Preparation
>
> Protein may be coupled to dye sol in a process involving passive adsorption. The protein may, for example, be an antibody preparation such as anti-alpha human chorionic gonadotrophin prepared in phosphate buffered saline pH 7.4 at 2 milligram/mi. A reaction mixture is prepared which contains 100 µl antibody solution, 2 mls dye sol, 2 mls 0.1M phosphate buffer pH 5.8 and 15.9 mls distilled water. After gentle mixing of this solution, the preparation is left for fifteen minutes at room temperature. Excess binding sites may be blocked by the addition of, for example, bovine serum albumin: 4 mls of 150 mg/ml BSA in 5 mM NaCl pH 7.4 is added to the reaction mixture, and after 15 minutes incubation at room temperature, the solution is centrifuged at 3000 g for 10 minutes, and the pellet resuspended in 10 mls

> of 0.25% (w/v) dextran/0.5% (w/v) lactose in 0.04M phosphate buffer. This antibody-dye sol conjugate is best stored in a freeze dried form.

May does not teach or suggest applying the blocking agent to any portion of the lateral flow strip. The cited passage is *not* concerned with non-specific binding to the lateral flow chromatography strip, as is the blocking strip of the claimed invention. To the contrary, May is concerned with non-specific binding to the antibody-sol conjugate. Hence, the context of May's "blocking" has nothing to do with either the ***structure*** or the function the claimed blocking strip.

The Examiner, on page 8 of the Office Action, asserts that the claimed blocking strip is "a mere functionally equivalent means" for providing blocking taught by May at col. 6, lines 45-57. In that cited passage, May recites:

> Following the application of the antibody to the detection zone, the remainder of the porous solid phase material should be treated to block any remaining binding sites elsewhere. Blocking can be achieved by treatment with protein (e.g. bovine serum albumin or milk protein), or with polyvinylalcohol or ethanolamine, or any combination of these agents, for example. The labelled reagent for the first zone can then be dispensed onto the dry carrier and will become mobile in the carrier when in the moist state. ***Between each of these various process steps (sensitisation, application of unlabelled reagent, blocking and application of the labelled reagent), the porous solid phase material should be dried***.

As illustrated by that passage, the blocking strip of the claimed invention is not equivalent means to the porous solid phase material of May. May's treatment to provide a single strip that is blocked requires eight steps, and includes numerous reagents. Each step must be taken sequentially, perhaps adding time, cost, and potentially error to the process.

The capillary matrix, as claimed herein, is also distinguishable from May's. The Examiner, on page 5 of the Office Action, cites May col. 18, lines 35-40, which relates not to oral assay devices, but to urine samples:

> Enzyme assays may be performed in which the anti-hCG antibody is conjugated to alkaline phosphatase, using conventional techniques, and diluted 1/100 in 0.01M phosphate buffered saline pH 7 containing 3% polyethylene glycol 6000, 1% (w/v) bovine serum albumin and 0.02% TRITON X305 (Trademark--obtainable from Rohm and Haas) before application to the sheet. Fresh urine samples are then applied, either directly from the urine stream, or by delivering an appropriate volume (e.g. 100 µl) from a container using a pipette, to the absorbent wick of the test device.

> Each sample is allowed to run for five minutes before a pad of liquid-swellable material soaked in BCIP substrate (at 1 mg/ml in 1M Tris/HCl pH 9.8) is placed in contact with the immobile antibody zone. After a further five minutes, the pad is removed, and colour generated read either by eye, or by using a light reflectometer.

The Examiner also cites May for the referral to treating "the member" with a surface active agent to enhance its ability to take up and deliver a moist sample rapidly and efficiently:

> It can be advantageous to pre-treat the member with a surface-active agent during manufacture, as this can reduce any inherent hydrophobicity in the member and therefore enhance its ability to take up and deliver a moist sample rapidly and efficiently. Col. 4, lines 43-57

In contrast, the capillary matrix of the claimed invention:

> [0051] ... can be routinely treated with a wetting agent (i.e., surfactant/detergent) and thereby rendered hydrophilic (wettable). However, since ***the capillary matrix is used in the oral cavity, it is required that the treating detergent be known not to be harmful to the subject mammal*** (e.g., human body) and preferably be approved for such use by the relevant regulatory authority (e.g., Food and Drug Administration).....
>
> [0052] ... it will be appreciated that other detergents can as well be used. It is only required that ***the detergent be safe for mammalian oral exposure***, not interfere with the test on lateral chromatographic strip C, and produce the required hydrophilic properties on the exterior surfaces of the matrix.

Additionally, because the claimed device is for oral insertion, and issue not addressed by May, the capillary matrix may also prevent backflow:

> [0054] From the foregoing, it should be clear that preferred capillary matrix materials have an interstitial spacing that facilitates uptake of ***oral*** fluid through capillary attraction in combination with adsorption on the material. This causes the oral fluid gathered ***from the mouth*** to be transported to the lateral chromatographic strip in preference to remaining in the mouth. At the same time, ***when the oral fluid arrives at the lateral chromatographic strip, it is absorbed to the strip in preference to remaining in the capillary matrix***.
>
> [0056] ... ***the capillary matrix can act as a barrier to back flow of reagents from the lateral flow chromatography strip back into the capillary matrix.*** This can be accomplished, for example, where the chromatography strip has a larger volume for fluid storage than the capillary matrix. In addition or alternatively, where the lateral flow chromatography strip is more hydrophilic than the capillary matrix ***the capillary matrix can also act as a barrier to backflow***.

These differences in function and structure illustrate that the claimed structures are not merely functionally equivalent means of May. May can not address backflow, because it is simply not an issue in the May technology. Moreover, there is no suggestion in May to apply its teachings regarding urine samples to an assay device for insertion into the mouth. It should be clear from this discussion that the structures of the claimed invention are patentably distinct limitations.

That May describes several analytes and kits does not overcome the major distinctions between May's and the claimed device, particularly when May's device is viewed as a whole.

The MPEP, at § 2141, instructs that "references must be considered ***as a whole*** and ***must suggest the desirability*** and thus the obviousness ***of making the combination***; ... references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and ... reasonable expectation of success is the standard with which obviousness is determined." Moreover, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

The test carrier in Schlipfenbacher teaches away or otherwise as a whole does not suggest the desirability of the claimed invention. In fact, the very purpose of Schlipfenbacher's device is at odds with the claimed invention, because Schlipfenbacher is drawn towards samples in which the analyte is highly concentrated:

> In order to make available an easily handled test carrier which is economic to produce and ***which is especially suitable for the evaluation of comparatively highly concentrated analytes***, for which immunological test carriers were previously not available, the present invention provides a test carrier for the analytical investigation of a sample liquid with the help of a specific binding reaction of two binding partners, of which a first is contained in the sample and a second is contained in the reagent system of the test carrier. Col. 2, lines 49-58.
>
> A ***reduction*** of the analyte concentration ***on*** the test carrier is thereby to some extent achieved without a separate previously provided dilution step being necessary. The carrier according to the present invention is advantageous for ***concentrations*** of above 10^{-8} mole/liter and especially of above 10^{-7} mole/liter. Col. 3, lines 27-33.
>
> The sample is ***usually*** a body fluid, such as ***blood or urine***. However, it can also be a liquid obtained by a preceding test step. Col. 1, lines 27-30.
>
> FIG. 2 shows a test carrier which, in an especially simple way, permits the determination of ***comparatively highly dosed parameters*** with an

> immunoenzymometric test principle. It is especially suitable for the ***determination*** of such ***parameters in a sample liquid which is available in comparatively large amounts, especially in urine***. Col. 7, lines 15-21.

In contrast, the claimed invention is directed to **oral** fluids, in which analytes are typically greatly diluted as compared to blood or urine. Indeed, it was known at the time the present application was filed that saliva contains approximately 500-fold less immunoglobulin than serum. Bakke et al., B191 abstract no. PoB 3601, 8 Int'l Conf AIDS (Jul 19-24, 1992) (Abstract provided herewith).

Additionally, the instant specification notes that unlike urine or the samples of Schlipfenbacher, oral fluids are not available in large amounts:

> [0009] Moreover, particularly with respect to assaying oral fluid samples, ***oral fluid is often in short supply***, particularly under circumstances where the test subject is stressed (e.g., when testing for drugs of abuse or life-threatening illnesses, which may make it difficult to use such multi-component assays. In addition, attempts to stimulate oral fluid production (e.g., by the use of citric acid or other salivation agents) result in ***increased saliva production*** which ***may actually dilute the analyte concentration***.

Hence, given this correct context of the assay devices, there is little in Schlipfenbacher that would lead one of skill in the art to either combine it with May or draw on it as a source of teachings for the claimed device.

Also note that Schlipfenbacher's Example 1, which addresses the properties suitable for "start zone 11" there is no discussion of the insertion of this member into the oral cavity, no discussion of toxicity, etc. Further regarding the "start zone":

> In use, the test carrier is dipped into the sample liquid to such an extent that only the start zone 21 is wetted. Thus, only the start zone makes contact with the sample liquid. Therefore, it must be such that it takes up the liquid spontaneously and completely and passes it on or gives it up well. For a test strip of the type here in question, it is important that all the zones placed after the start zone 21, which form the actual functional range of the test carrier, are supplied sufficiently and reproducably with liquid. This can be achieved by leaving the test carrier to stand in a vessel with the sample so that a continuous contact is present to a large supply of liquid. However, this makes the handling difficult. Therefore, it is desirable that the start zone 21 takes up a sufficient amount of liquid within a few seconds and, according to the test requirements, again gives it off after the test strip has been taken out of the sample liquid. Col. 7, lines 39-56

Again, there is nothing in this description to suggest that the Schlipfenbacher "start zone" is suitable for oral contact, in contrast to the capillary matrix of the claimed invention.

The Examiner, on page 6 of the Office Action, asserts that "Schlipfenbacher teaches providing a blocking strip (23) containing a buffer and a conjugate strip (24) between a collection strip and an assay strip. See column 8, lines 23-31." The cited section reads:

> The further zones contain the same reagents as described in FIG. 1 for the case of an immunoenzymometric test. The auxiliary reagent zone 23 contains a buffer and optionally further ***adjuvant*** reagents, the conjugate zone 24 an enzyme conjugate of a (second) binding partner specifically bindable with the analyte, the fixing zone 25 solid-phase-bound analyte (or analyte analogue) and the colour-forming zone 26 a colour-forming substrate of the labelling enzyme. Col. 8, lines 23-31.

It is not clear from this reading what is contained on "auxiliary reagent zone" or how the buffer or un-recited adjuvant reagents block either nonspecific binding or back flow. The Examiner also asserts that "The reagents on the blocking strip 23 comprise sodium phosphate buffer and bovine serum albumin to prevent non-specific binding. See column 11, lines 1-11." This cited passage reads:

> Buffer Zone 23
>
> A fleece material SL 4207 KA of the firm Kalff, Euskirchen, Federal Republic of Germany, consisting of 90% polyester, 10% regenerated cellulose and a small amount of acrylate, with a thickness of 0.7 mm and an absorptive capacity of 480 ml/m^2, was impregnated with the following solution and subsequently dried:
>
> 200 mM sodium phosphate, pH 7.8
>
> 1% bovine serum albumin.

There is no indication, however, that this passage refers to blocking, or what possible function the serum albumin might have. Indeed, serum albumin is included in the substrate of the conjugate strip:

> Conjugate Zone 24
>
> A glass fibre fleece of 100 parts by weight of glass fibre, consolidated with 10 parts by weight of Kuralon, in a thickness of 0.2 mm and with an absorption capacity of 200 ml/m^2, was impregnated with the following solution and subsequently dried:
>
> 70 mM sodium phosphate, pH 7.4
>
> 1% trehalose
>
> 0.5% bovine serum albumin
>
> 6 kU/liter conjugate of β-galactosidase and analyte-specific antibody (IgG)

70 mg./l unlabelled analyte-specific antibody (IgG) as capturing reagent. Col. 11, lines 12-35.

Because Schlipfenbacher states that "the present invention is especially concerned with enzyme immune tests in which an enzyme label is used. The labelling enzyme is usually detected by the colour-forming reaction of a substrate of the labelling enzyme," col. 2, lines 37-40, and because BSA is well known as a stabilizing reagent in enzymatic reactions, including those involving β-galactosidase, the function of the BSA in Schlipfenbacher and is ambiguous. To support an obviousness rejection, Schlipfenbacher must be taken as a whole, or at least a sum of its many parts, instead of reliance on disjointed terms like "buffer" or "bovine serum albumin".

Applicants respectfully submit that May and Schlipfenbacher, taken alone or in combination, fail to render the claims obvious. Indeed, given the distinct nature of the samples for analysis in these devices (e.g., concentrated analytes in large volumes of sample) when compared to the claimed device, there is nothing to suggest their combination, and nothing to suggest that they would provide for a reasonable expectation of success. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the § 103 rejection of these claims.

Moreover, the Court has instructed that objective evidence relevant to the issue of obviousness, i.e., secondary factors, ***must*** be evaluated by Office personnel. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Such evidence may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results.

For example the Applicants' assignee, OraSure Technologies, has played an instrumental role in increasing access to HIV testing throughout the world. In 1994, OraSure brought to market the OraSure® HIV-1 Oral Fluid Specimen Device - the ***only*** FDA approved collection device that collects oral fluid to test for antibodies to the HIV-1 virus. Then, in 2004, OraSure launched the first oral fluid rapid HIV test - the OraQuick ADVANCE® HIV-1/2 Antibody Test - the only FDA approved test than can be used on oral fluid, plasma, fingerstick and venipuncture whole blood specimens. Both of the Examiner's cited references date back to 1988, after the identification of HIV, yet the claimed invention provides for the only oral fluid test for HIV. As such, the claimed invention has demonstrated the failure of others, unsolved needs, and commercial success. It is clear that claimed

invention reflects an advancement and "real innovation." *KSR Int'l. Co v. Teleflex Inc.*, No. 04-1350 (April 30, 2007) at 15.

CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly requested. The Commissioner is hereby authorized to charge any payment deficiency to Deposit Account No. 19-2380. Should the Examiner have any questions that would facilitate further prosecution or allowance of this application, the Examiner is invited to contact the Applicants' representative designated below.

Respectfully submitted,

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Sources of error in HIV testing of saliva samples.

Bakke AC, Seymour E, Adair SM, Fitzgibbons D, Lealos R, Stramer S.

Int Conf AIDS. 1992 Jul 19-24; 8: B191 (abstract no. PoB 3601).

Oregon Health Sciences U., Portland.

OBJECTIVES: Difficulties in collection of blood have made the use of saliva desirable for HIV testing. However, several potential sources of error exist in saliva testing and we have investigated several of these including: relative HIV antibody concentration, microbial contamination of saliva, long-term stability of saliva samples, and effect of collecting several saliva specimens sequentially. METHODS: Sequential saliva specimens were collected using a recently developed collection device called the Omni-Sal. Matched serum samples were obtained by routine venepuncture. All specimens were screened for HIV antibodies using the Abbott serum antibody HIV-1 EIA kit. RESULTS: Saliva contains approximately 500-fold less immunoglobulin than serum. The average titer for saliva HIV antibodies was 1:19, while the average titer for matched serums was approximately 1:10000. This difference necessitated optimization of the HIV test kit for saliva. Using serum as the gold standard and the serum cutoff value as described in the Abbott kit, the saliva test was 99.9% sensitive and 99.9% specific. Secondly, stability studies have shown that the saliva specimen diluent prevents bacterial growth which would degrade the HIV antibody. In addition, optical densities were stable for 96 hr at 37 degrees C, for 7 days at 4 degrees C and for at least 9 months at -40 degrees C. Finally, sequential collection of saliva specimens decreases the quantity of HIV antibody in the specimen. Forty of 50 sequential, second collections showed a decrease in the O.D. When a third specimen was collected, 100% had a decreased O.D. CONCLUSIONS: Several potential sources of error exist in saliva HIV testing. These can be controlled by stabilizing the specimen and enhancing the serum HIV test system. Importantly, when saliva is sequentially collected within a short period of time, the quantity of HIV antibody decreases. This implies that the rate of immunoglobulin secretion into saliva is lower than the rate of saliva production.

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